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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/718,102	11/20/2000	Maria-Grazia Roncarolo	DX0261K1B	9698

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EXAMINER
HAMUD, FOZIA M

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 07/30/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/718,102	Roncarolo et al
Examiner	**Art Unit**
Fozia Hamud	1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) [X] Responsive to communication(s) filed on *Feb 21, 2002* .

2a) [ ] This action is **FINAL.** 2b) [X] This action is non-final.

3) [ ] Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) [X] Claim(s) *2-5 and 15-27* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) [ ] Claim(s) _____ is/are allowed.

6) [X] Claim(s) *2-5 and 15-27* is/are rejected.

7) [ ] Claim(s) _____ is/are objected to.

8) [ ] Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) [ ] The specification is objected to by the Examiner.

10) [ ] The drawing(s) filed on _____ is/are a) [ ] accepted or b) [ ] objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) [ ] The proposed drawing correction filed on _____ is: a) [ ] approved b) [ ] disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) [ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) [ ] Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) [ ] All b) [ ] Some* c) [ ] None of:

1. [ ] Certified copies of the priority documents have been received.
2. [ ] Certified copies of the priority documents have been received in Application No. _____ .
3. [ ] Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) [ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) [ ] The translation of the foreign language provisional application has been received.

15) [ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) [X] Notice of References Cited (PTO-892)
2) [ ] Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) [ ] Information Disclosure Statement(s) (PTO-1449) Paper No(s). ___
4) [ ] Interview Summary (PTO-413) Paper No(s).
5) [ ] Notice of Informal Patent Application (PTO-152)
6) [ ] Other:

DETAILED ACTION

1. Claims 1, 6-14 and 28-30 have been canceled in the preliminary amendment filed on 24 July 2002, in Paper No.5 Thus claims 2-5 and 15-27 are pending and under consideration by the Examiner.

Information Disclosure Statement:

2a. Applicants filed an information disclosure statement on 21 February 200, which was entered as Paper NO:9. Applicants submitted copies of references AI and BD and requested that all of the other references filed with the parent case, U.S. Application Serial Number 08/643,810 be considered. None of the references have been considered, because the PTO 1449 form filed with the instant case comprises only two pages, (pages 3 and 4 which list references BG to CQ). It appears that pages 1 and 2 are missing. All of the references filed with the parent case, (including references AI and BD) will be considered, once Applicants file complete PTO 1449 form listing all the references. Applicant does not need to submit copies of the references.

Priority:

2b. Applicants desire the benefit of an earlier filing date under U.S.C. 120 and the first sentence of the specification contains a specific reference to the prior Application 07/784,208. However, instant Application is a divisional of 08/648,810 filed on 05/06/1996 (U.S. Patent 6,277,635) which is continuation in part of 07/784,208 filed on 03/04/1992. Therefore, instant case is afforded the filing date of the parent case, 08/648,810, which was filed on 05/06/1996. The first sentence of the specification should be corrected to reflect this.

2b. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3a. Claims 20-27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention.

Although independent claim 15 (from which claims 20-27 depend) is enabled, instant specification does not provide enablement for dependent claims 20-27. Claims 20-27 are drawn to "a method of suppressing a response in a T cell to an antigen, comprising administering to an immune system a combination of interleukin 10 (IL-10) and an antigen or anti- CD3 antibodies, wherein said response accompanies tissue transplantation", however, although instant specification teaches that IL-10 induces T cell anergy in alloantigen-specific and anti-CD3 stimulated CD4+ T cells , and inhibits the production of IL-2, IFN-γ, IL-5, TNF-α, GM-CSF by these cells, (see page 53, line 27 through page 54 line 19, 59, lines 5-30), it does not disclose a method of suppressing a response which accompanies tissue transplantation by administering to an immune system a combination of IL-10 and an antigen or anti- CD3 antibodies. The specification discloses that IL-10 renders T cells anergic and this is not reversed by addition of IL-2, and that the signaling through the TCR/CD3 complex is selectively impaired in IL-10 anergized T cells, (page 59, lines 31-36). The

specification discloses that human SCID patients are one of the few examples in which in vivo tolerance is obtained after HLA mismatched transplantation, and these host reactive T cells secrete high levels of IL-10 in vitro and that high levels of IL-10 hve been observed in vivo, suggesting a role in the induction and maintenance of tolerance, (see page 60, lines 19-30). This is the only connection established between IL-10 and tissue transplantation in the instant case. The specification speculates that IL-10 may play a role in the induction and maintenance of tolerance, because high levels of IL-10 are secreted by host reactive T cells and also high levels of IL-10 have been observed in vivo, (see page 61, lines 25-29). On the same page, the specification states that "it is tempting to conclude that high levels of IL-10 observed in the SCID patients render the host-reactive T cells anergic in vivo". It also states that high levels of IL-10 secretion prior to transplantation have been shown to correlate with a successful outcome of the transplant. However, beyond these statements, instant specification does not present any data showing that the administration of IL-10 with an antigen or with anti-CD3 antibodies indeed suppresses response which accompanies tissue transplantation, especially after organ or bone marrow transplantation. The criteria set forth in Ex parte Forman (230 USPQ 546 (Bd. Pat. App. & Int. 1986), and reiterated in In re Wands (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)), which include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims, is the basis for determining undue extermination. In the instant application, it would be unpredictable whether the administration to an immune system a combination of IL-10

and an antigen or anti- CD3 antibodies, would suppress a response which accompanies tissue transplantation, because there is no data presented in the instant case demonstrating that administration of IL-10 with an antigen or with anti-CD3 antibodies to an immune system suppresses a response which accompanies tissue transplantation. Furthermore, there is no guidance provided by Applicants, as to how much is an effective amount of IL-10 or what antigen from the mammal, how often should said amounts be administered. Therefore, one of ordinary skill in the art would not be able to predict whether the administration of IL-10 with or an antigen or with anti-CD3 antibodies would suppress a response in a T cell which accompanies organ or bone marrow transplantation, given the lack of guidance by instant specification. Therefore, Applicants must present evidence that the administration to an immune system a combination of IL-10 and an antigen or anti- CD3 antibodies, would suppress a T cell response, wherein said response accompanies tissue transplantation, in order to satisfy 35 U.S.C. 112, first paragraph.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4a. Claims 2-5, 15-27 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4b. Claim 2 recites "a method of inhibiting by an immune system an antigen specific response .....comprising administering to said immune system....", however the claim is vague and indefinite,

because it is unclear exactly what is being claimed. Does the immune system inhibit an antigen-specific response, or does the administration of IL-10 and an antigen inhibit the immune system to respond to subsequent presentation of said antigen? Applicant must clarify the claim.

4c. Claim 3 (b) is vague and indefinite, because it is unclear what is ".....proliferative response of CD4+ host reactive T cell". Does this mean that the administration of IL 10 and an antigen inhibit CD4+ T cell proliferation? Or does it mean that said administration inhibits CD4+ T cells to stimulate proliferation of other cells? And are these T cell clones in a patient or in a tissue culture dish?

4d. Claim 3 [c] is also vague and indefinite, because it is unclear whether "said inhibiting" refers to the "inhibiting" recited in claim 2 or to the "inhibiting" recited in 3(b).

4e. Claim 4 recites, "..... amount sufficient to decrease responder T cell activation...", this render the claim vague, because it is not understood what "..responder T cell activation" mean. Appropriate correction is required.

4f. Claim 5 is unclear, does the inhibition of T cells lead to reduced stimulatory capacity of pbmc, dendritic cells, monocytes and/or B cells? "Stimulatory capacity", for what? What stimulation is being inhibited?

4g. Claim 15 recites " a method of suppressing in a T cell response....comprising administering to an immune system..", is the T cell in a subject or is it introduced into the subject, what response? how is said administration of IL-10 and antigen is carried out into the immune system, i.e how could the immune system be separated from the individual?

4h. Claim 19 recites "suppresses response to subsequent stimulation", subsequent stimulation to what, what is being stimulated?, what subsequent response is being suppressed?

4i. Claim 20 recites "said response accompanies tissue transplantation...", what response? Is it transplant related complications or what?

4j. Claim 23 recites "...said T cell is introduced to the recipient of said tissue transplantation? How is this T cell introduced to said patient and what is the propose of introducing said T cell? Furthermore, is the response to be suppressed within the T cell that is introduced or T cell in the subject?

Claim rejections-35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 2-5, 15-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Rott et al (1994).

Rott et disclose a method of inhibiting an antigen-specific T cell responses to subsequent presentation of said antigen by administering IL-10 and said antigen. Rott et al used a rat model of encephalomyelitis (EAE), an autoimmune disease mediated by myelin basic protein (MBP), which leads to subsequent activation of autoantigen-specific CD4+ T cell responses. The researchers showed that upon systemic administration during the initiation phase of disease, IL-10 was effective in markedly suppressing the subsequent induction of EAE in Lewis rats, (see abstract and page 1437, column 1). The researchers administered IL-10 in MBP-immunized rats by subcutaneous injection

at days 0, 3, and 6 after immunization, and showed that IL-10 strongly suppressed the subsequent occurrence of clinical EAE, (see page 1437, column 1 and figure 4). Rott et al also demonstrated that MBP-specific T cell responses from IL-10 treated animals displayed diminished proliferative capacity when compared to controls, (see page 1437, column 2) and that IL-10 was capable of markedly suppressing the class II up-regulation of IFNγ-treated rat peritoneal macrophage *in vitro*, (see page 1436, column 1). They also showed that IL-10 could reduce even the constitutive class II expression on non activated macrophage after incubation period of 24 hours, (see figure 1B).

Instant claims 2-5 are interpreted as being drawn to a method of inhibiting an antigen specific response to subsequent presentation of said antigen in a subject, said method comprising administering to said subject an effective amount of IL-10 and said antigen, wherein said immune response is mediated by macrophages, APC, Langerhans cell or dendritic cell, and further inhibiting proliferative response of CD4+ host reactive T cells.

The Rott et al reference anticipates instant claims 2-5, because Rott et al disclose a method of inhibiting subsequent induction of EAE, by administering IL-10 to rats that had been immunized with MBP, Rott et al also demonstrated that MBP-specific T cell responses from IL-10 treated animals displayed diminished proliferative capacity when compared to controls. The T cell response stimulated by MBP is mediated by macrophages.

Claims 15-19 are interpreted as being drawn to a method of suppressing a response in a T cell to a self antigen restricted by MHC molecules, said method comprising administering to a subject IL-10 and an antigen or anti-CD3 antibodies. Rott et al reference clearly anticipates claims 15-19,

because it teaches that administration of IL-10 and MBP to rats suppresses the subsequent induction of EAE in Lewis rats. MBP is a self antigen and its responses are mediated by MHC II molecules.

Therefore, the Rott et al reference anticipates instant claims 2-5 and 15-19, because it meets all the limitation recited in said claims.

Conclusion

5. No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fozia Hamud whose telephone number is (703) 308-8891. The examiner can normally be reached on Mondays and Thursdays and every other Friday from 8:00AM to 4:30PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary kunz can be reached at (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4227. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Fozia Hamud
Patent Examiner
Art Unit 1647
25 July 2002

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